Remarks

The purpose of this Amendment is to place this application into condition for allowance or better position for appeal. MPEP 714.13. Claims 35 and 56-66 are pending. Claims 35, 65 and 66 are currently amended. The remaining claims other than claims 35, 65 and 66 have previously been canceled or are canceled without prejudice herein. Claim 35 has been amended to include the subject matter of old Claim 64 and claims 65 and 66 are amended to depend from a pending claim (claim 35). Applicants submit no new matter has been added and request entry of the amendment.

The Examiner's previous rejection fails to adequately consider the separate patentability of Claims 64, 65 and 66 (claims 35, 65 and 66, as amended). As will be explained below, these claims are patentable over Neer, et al. Accordingly, the amendment places this application in condition for allowance. Reconsideration of the application is respectfully requested.

Rejection Under 35 U.S.C. Section 112, First Paragraph

Claims 59-63 were rejected under the first paragraph of Section 112. Applicants have cancelled claims 59-63 thereby rendering this rejection moot.

Rejection Under 35 U.S.C. Section 102(b)

Claims 64-66 (claims 35, 65 and 66, as amended) have been rejected under 35 U.S.C. § 102(b) as being anticipated by Neer, et al. (Neer). Applicants respectfully disagree. Neer doesn't anticipate the present claims, at least for the reasons set forth below.

Summary of Argument

The claimed invention is based on a revolutionary new method of treating human patients for osteoporosis. Applicants discovered that PTH(1-34) administered daily at a 20 microgram dose reduces the risk of fracture in both

vertebral and non-vertebral bone in human subjects. A decrease in certain undesirable side effects has also been observed at the claimed 20 microgram dose. Applicants' discovery is a major advance over Neer, which discloses a method of administering an unknown microgram dose of PTH(1-34) to a small population resulting in an increase in trabecular bone density but no consistent change in cortical bone density (see: Neer, column 10, lines 11-15).

Neer discloses administration of certain unit dose ranges of PTH(1-34) to subjects. However, how the units disclosed in Neer convert to dosages in micrograms is unknown and unknowable because Neer fails to disclose essential information-a specific activity for the PTH(1-34). In addition to Neer's failure to disclose a specific activity, one cannot look to extrinsic evidence to determine the specific activity of PTH(1-34) because there is no such standard. Rather, the literature shows as much as a five-fold variance in such specific activity values rendering one unable to identify which specific activity (if any) was applicable to Neer.

Furthermore, Neer's method of increasing bone mass fails to demonstrate a reduction in the risk of both vertebral and non-vertebral fractures. Although Neer identifies a dosage range as broad as 100-700 units/day, Neer discloses no data to demonstrate that administration of any dose in that range has any effect on vertebral and non-vertebral bone fracture, as currently claimed. According to Example 2, Neer's 500 unit dose exhibited no change in cortical bone density (see: column 10, lines 11-15). In contrast, the present invention is directed to a dosage that is administered to a patient to reduce the risk of both vertebral and non-vertebral bone fracture.

Therefore, Neer does not anticipate the present invention at least because it does not disclose Applicants' claimed 20 microgram dose directed to a reduction in the risk of fracture in both vertebral and non-vertebral bone.

Neer Alone Fails To Disclose The Specific Activity for PTH(1-34)

In order to covert the "units" of PTH(1-34) disclosed in Neer to micrograms of PTH(1-34), one must first ascertain the conversion factor or "specific activity" of the PTH(1-34) substance being tested.

Accurate conversion of units to micrograms requires either one of the following procedures:

1. Application of ***the*** specific activity relationship for the **particular PTH sample** under consideration as provided in the particular reference, or

2. Experimental derivation by measurement of units of activity in the ***specific assay*** **and** ***specified standard*** stipulated by the reference.

Neer states that units of activity were measured in the chick hypercalcemic assay (Col 5), and that "units are defined in terms of the International Reference Preparation of hPTHF 1-34" (Col 5). However, Neer itself fails to disclose a specific activity value for hPTH(1-34). The Examiner does not dispute this fact. The Examiner has not presented evidence that the specific activity value can be experimentally determined in view of Neer's teachings. In fact, the Declarations of Meiklejohn and Griffith provide evidence that such specific activity determinations cannot be determined in view of Neer.

Specifically, Meiklejohn declares that he does not believe that there currently is or has ever been an appropriate International Reference Standard for human PTH(1-34). Meiklejohn further declares that he is not aware of the existence of the specified International Reference Preparation of human PTH(1-34) cited by Neer. If Neer's Preparation is not publicly accessible, Griffith declares that one could not

determine the microgram equivalent of Neer's unit dosage, nor compare Neer to other data.

Specific activity measurements for PTH are in fact sensitive to the particular assay used and the particular standard used for calibration. Without access to the specific reference standard stipulated by Neer, there is *no way* to adequately interpret or convert Neer's dosage to micrograms. Applicants have produced evidence demonstrating that one cannot determine Neer's specific activity of its disclosed and tested PTH(1-34) substance. The Examiner has not provided evidence to rebut Applicants' evidence. Accordingly, the rejection should be withdrawn.

Neer In Combination With External References Fails To Disclose The Specific Activity for PTH(1-34)

As an alternative to experimental determination of Neer's reference standard, the Examiner asserts that one can make determinations based on a separate reference standard from the literature. For example, in the Office Action dated November 12, 2002, a conversion factor of 25 micrograms = 400 units is proposed.[1] In the Final Action, a conversion of 40 micrograms = 500 units is proposed. In addition, it is proposed that a specific activity can be generated by averaging the twelve specific activity values disclosed by Applicants in Paper 10 (see Table 1 *infra*).

The issue, however, is not whether *a* specific activity value could be conjured up, or imported from somewhere, to interpret Neer; the issue is whether a skilled artisan could ascertain or determine the *particular* specific activity value for the specific PTH(1-34) in Neer. Applicants have provided unrebutted evidence that determination of the Neer specific activity is not possible. Accordingly, Neer cannot anticipate the present invention.

[1] November 12, 2002 Office Action, paper no. 9, page 5. It appears that this conversion factor was taken from Lindsay, et al. (IDS code CB); Lindsay, et al (IDS code CD) and Lane, et al. (IDS code CE)

No reasonable basis exists for selecting one specific activity over another. As an example of why picking and choosing from the various specific activities in the literature is inappropriate, assume that the Examiner chose to rely on Sone's specific activity (3 U/μg; IDS reference CAA) to interpret Neer's specific activity. A range of 33.3 - 233.3 μg would have resulted, and Applicants' claimed dose of 20 μg/day would also clearly fall outside the scope of this arbitrary range.

The chosen separate reference values are broadly dispersed over a range of values, e.g. 3 U/μg to 16 U/μg, making it virtually impossible to discern Neer's specific activity value. The Examiner inappropriately asserts on Page 7 of Paper 14 that these published specific activity values of PTH(1-34) are "quite close to each other and quite consistent." To the contrary, the cited references demonstrate more than a five-fold variance from lowest to highest published specific activity values for PTH(1-34). In addition, the Examiner cites no rational basis for averaging these numbers from different sources to arrive at the specific conversion factor applicable to the PTH(1-34) disclosed by Neer. Randomly choosing a specific value from the art, or taking an average value from the art does not accurately represent Neer's specific activity value.

It is hornbook law that anticipation must be found in a single reference. *Studiengesellschaft Kohle, m.b.H. v. Dart Industries*, 726 F.2d 724,726-27 (Fed. Cir. 1984). According to the MPEP, extra references or extrinsic evidence may be used in deciding the issue of anticipation to explain but not expand the meaning of a reference. MPEP 2131.01. See *In re Baxter Travenol Lab* 21 USPQ2d 1281, 1284 (Fed. Cir. 1991). However, the Examiner's use of extra references in the present case is entirely inappropriate.

The Examiner has not established a *prima facie* case of anticipation in part because he has failed in meeting his

burden to show that Neer discloses a 20 microgram dose of PTH(1-34). The arbitrary selection of a conversion factor apparent from the three different proposals discussed above is improper to establish anticipation. Applicants respectfully request that the Examiner withdraw the rejection.

Neer's Dosage Ranges Do Not Anticipate Applicants' Claimed Dose

Applicants' invention is directed to a particular dose producing unexpected clinical results and is patentable in view of Neer. A skilled artisan (again assuming for argument one of the Examiner's conversion methods are reliable) would assume from Neer that the preferred dosage of 500 units represented an optimal dose, maximizing clinical benefit (e.g. increased spinal BMD) and minimizing adverse effects. However, Neer's preferred dose (500 units), and the only tested dose, doesn't anticipate the presently claimed dose under any of the Examiner's interpretations (Method 1, 16 units = 1 μg so 500 units = 31 μg; under Method 2, 12.5 units = 1 μg so 500 units equals 40 μg; under Model 3, 500 units = 46.2 μg).

In addition, according to the MPEP, if the claims are directed to a narrow range, the reference teaches a broad range, and there is evidence of unexpected results within the claimed narrow range, it may be reasonable to conclude that the narrow range is not disclosed with sufficient specificity to constitute an anticipation of the claims. MPEP 2131.03. The Examiner's position rests on derivation of various generic dosage ranges (in micrograms) (Table 1). As previously noted, three different methods have been proposed to convert units to micrograms. These methods are represented in Table 1.

Table 1.

	Neer's disclosed dosage range ("Units")	**Examiner's proposed specific activity**	**Examiner's derived range (micrograms)**
Method 1	100 - 700	16 Units/μg[2]	6.3 - 43.8
	200-600		12.5 - 37.5
	400 - 500		25 - 31.3
Method 2	100-700	12.5 Units/μg[3]	8.0 - 56.0
	200-600		16.0 - 48.0
	400-500		32.0 -40.0
Method 3	100-700	Avg. = 10.8 units/μg[4]	9.2-64.8
	200-600		18.5-55.5
	400-500		37.0 -46.2

The narrow range - a specific dose of 20 μg - is not disclosed with sufficient specificity by the Neer genus of doses to be anticipated. MPEP 2131.03.

Furthermore, Applicants' claimed invention is patentable over Neer for additional reasons.

20 μg dose produced clinical benefits not observed in Neer

Unlike Neer, Applicants discovered and claim that 20 μg/day reduced the risk of vertebral and non-vertebral bone fracture. Neer discloses that administration of PTH(1-34) increased bone mineral density (BMD) in the spine, but produced *no change* in non-vertebral bone. Specifically, Neer

[2] Office Action, November 12, 2002, Paper No. 9.
[3] Final Action, July 30, 2003, Paper No. 14.
[4] The Examiner calculated an average of specific activity values cited in 12 references in Applicants' IDS. Specifically, the values are: 12.5 U/μg; 12.5 U/μg; 12.5 U/μg; 3.3 U/μg; 15 U/μg; 16 U/μg; 16 U/μg; 16 U/μg; 5 U/μg; 7.5 U/μg; 10 U/μg; and 3 U/μg taken respectively from IDS references CAH, CAG, CAE, CL, CN, CE, CB, CD, CO, CO, CU, and CAA.

observed "*no consistent change*" in BMD of non-spinal bone, i.e. the forearm (See column 10).

Prior to Applicants' invention there was no evidence of reduced fracture associated with the administration of PTH. Indeed, prior to Applicants' invention there was not even a correlation between increased BMD and reduced fracture on administration of PTH.[5] While Neer showed an increase in BMD in spinal bone there was no change observed in non-vertebral bone. Neer provides no expectation of reduced fracture risk anywhere in the body, let alone in non-vertebral bone.

The 20 μg/day dose resulted in a decrease in certain undesirable side effects

In addition to discovering that a dose of 20 μg/day is effective in reducing the risk of bone fracture, Applicants have discovered that these effects can be achieved with a decrease in certain undesirable side effects (see specification at page 52). According to the attached article supported by Lilly and published in *The New England Journal of Medicine*, 40 μg/day dose of Lilly's PTH(1-34) "was more likely to have side effects" and more likely to result in patients being withdrawn from this particular study due to an adverse event (6% of patients withdrew in the placebo and 20 μg/day dose groups while 11% of patients withdrew in the 40 μg/day dose group). N Engl J Med 2001; 344 at 1434 and 1438.

For example, the incidence of hypercalcemia is stated to have occurred in 3% of women receiving 20 μg/day and 11% of the women in the 40 μg/day dose group. Treatment was withdrawn because of repeatedly elevated serum calcium concentrations in one woman in the 20 μg/day dose group compared to nine in the 40 μg/day dose group. *Id.* at page 1439. The Examiner is encouraged to read this article, especially the Adverse Events section beginning on page 1437.

[5] In their previous response (Paper 13) filed February 14, 2003, Applicants cited references that teach no correlation between increased BMD and reduction in the risk of bone fracture on the administration of PTH. Cf. Riggs, IDS code CX; Hodsman, IDS code CAI.

In addition, according to the Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document (attached and available at: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3761b2_01_lilly.pdf), "There were significant increases in the incidence of headache and nausea compared with placebo that were consistent with previous studies evaluating doses higher than 20 μg/day." See pages 93 and 94. The Examiner is also encouraged to read this document, especially pages 84-113 of the Clinical Safety section.

Conclusion

Applicants' claimed invention is patentable in view of Neer. The literature shows as much as a five-fold variance in PTH(1-34) specific activity values rendering one unable to identify which specific activity (if any) or microgram dose was applicable to Neer. Furthermore, Neer's method of increasing bone mass fails to demonstrate a reduction in the risk of both vertebral and non-vertebral fractures as currently claimed. Applicants submit that each point of the rejection has been adequately addressed and, in view of the amendment and remarks, respectfully requests withdrawal of the rejection and passage of the application to issuance. The Examiner is encouraged to contact the undersigned with any questions.

Respectfully submitted,

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